Genetic determinism in mental retardation. Etiologic diagnosis steps

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ABSTRACT:

Introduction: establishing the etiology of diseases with genetic causes is a difficult action and it’s represent a continuous challenge for all who deal with this problem. Only identify the cause can help us to determine prognosis and genetic counseling of a right.

Purpose: this paper attempts to outline the various etiologies of mental retardation and steps to follow in order to establish an etiologic diagnosis correctly.

Material and method: There are underlined the importance of knowing family history, dismorphological examination, sometimes oriented diagnosis (42% of children with retardation have three or more chromosomal abnormalities), neurological examination and tests targeted based on abnormalities found, psychological examination, specific genetic testing: performing karyotype, FISH examination (for studying subtelomeric abnormalities), molecular studies (for possible fragile X syndrome), targeted studies for metabolic diseases.

Conclusions: the main genetic cause of mental retardation, regardless of severity, is represented by chromosomal abnormalities, which can be numerical or structural, of these, Down syndrome is the most frequently encountered, followed by 2% fragile X syndrome, deletion of subtelomeric regions (4.4%), metabolic diseases 1%.

Key words: mental retardation, etiology, genetic determinism

REZUMAT:

Introducere: stabilirea etiologiei de boli cu cauze genetice este o acțiune dificilă și se reprezintă o provocare continuă pentru toți cei care se ocupă cu această problemă. Identificarea cauzei ne poate ajuta în a determina prognosticul și consilierea genetică.

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**Scop:** această lucrare încearcă să contureze diverse etiologii de retard mental și pașii de urmat în scopul de a stabili un diagnostic etiologic corect.

**Material și metodă:** S-a subliniat importanța cunoașterii istoriei familiei, a examinării dismorfolologica, care orientează diagnosticul (42% din copii cu retard au trei sau mai multe anomalii cromozomiale), examenului neurologic și testelor specifice bazate pe anomalii constatate, examenului psihologic, testului genetic specific: efectuarea cariotipului, examenul FISH (pentru studierea anomalii subtelomerice), studii moleculare (pentru sindromul X fragil este posibil), studii specifice pentru boli metabolice.

**Concluzii:** principala cauză genetică de întârziere mentală, indiferent de severitate, este reprezentată de anomalii cromozomiale, care pot fi numerice sau structural. Dintre acestea, sindromul Down este întâlnit cel mai frecvent, urmat la 2% de sindromul X fragil, eliminarea din regiunile subtelomerice (4,4%), boli metabolice 1%.

**Cuvinte cheie:** retard mental, etiologie, determinismul genetic.

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**Mental retardation (MR)**

Incomplete development of intelligence, characterized by lack of cognitive skills, communication, motor and social development occur during in developmental period (by ICD 10).

MR diagnosis is made by determining the intelligence quotient (IQ) and adaptive assessment functions (mental retardation is mean IQ below 70).


**Introduction**

Elucidation of etiology mental retardation must contain 10 investigations:

1. Clinical history
2. Family history
3. Dismorfolologic examination
4. Neurologic examination
5. Karyotype
6. FISH for subtelomere abnormalities
7. Fragile X molecular genetic testing
8. Molecular genetic testing
9. Brain imaging
10. Metabolic testing (Covic et al., 2004)

Approach to the clinical genetics evaluation for DD/MR, Pediatrics, 2006

Family history (Covic et al., 2004; Dobrescu, 2005; van Karnebeek et al., 2005)
RM occurs mainly in children who have a family history similar damage
This raises the performance requirement tree (ranging up to 3 generations)
Neurological examination

In support of etiologic diagnosis, clinical examination, neurological and psychological examination are important. In over 50% of cases, people may have associated neurological MR: Cerebral palsy, microcephaly, seizures also hearing disorders are associated in more than 10% of cases, conduct disorder, irritability, fits of anger. (Covic et al., 2004)

Diagnosis

Medical history, dismorfisologic and neurological examination (extended by the anomalies identified) are followed by genetic testing, targeted the suspected pathology.

- **Chromosomal examination**: perform karyotype, molecular cytogenetic techniques - FISH (fluorescent in situ hybridisation), highlighting microdeletions / duplications, rearrangements of subtelomeric.
- **FRAXA site** (excluding testing for fragile X syndrome cases with microcephaly)
- **Metabolic screening** (Covic et al., 2004; Todoran et al., 2008)

Dismorfologic examination:

*Measurements*: height, weight, head perimeter, states, body measurements, eyes, ears, chest circumference, the intermamelonar distance.
Minor malformations: head shape, craniofacial dismorfism, mouth, teeth, palate veil, neck, limbs, fingers, fingerprints, external genitalia, skin - hypo-/hyperpigmentations.

- dolicocefaly
- macrocephaly
- mycrocephaly

Hypotelorism      hypertelorism      brachycephaly

Recognition of clinical syndromes based on dismorphology (van Karnebeek et al., 2005)

Known genes: short stature, microcephaly, hirsutism, MCC, MR, autistic features (eg Rubinstein Taybi Syndrome); stature, macrocephaly (eg Sotos syndrome, Ruvalcaba Bannayan Rily syndrome)

Unknown genes: eg Kabuki Syndrome

Sotos Syndrome

Autosomal numerical anomalies are more common than the heterozom anormalies
There is a predisposition to male. 42% of children with MR has three or more chromosomal abnormalities (Covic et al., 2004; van Karnebeek et al., 2005; Moescher et al., 2006)

**Chromosomal abnormalities:** are the most common cause of severe MR ~ 40% and 10% cause of easy mental retardation.

a) numerical chromosomal abnormalities

*Autosomal:* 21Trisomy (47, XX, 21) - Down syndrome, 13 Trisomy (47, XX, +13 or 47,XY,+13) – Patau syndrome, 18 Trisomy (47, XX, +18) - Edwards syndrome, 8 Trisomy (47, XX, +8)

Down syndrome

Patau Syndrome
Heterosomal numerical anomalies: (Todoran et al., 2008)

Turner syndrome (45, X), Klinefelter syndrome (47, XXY), XYY syndrome, Triplo X Syndrome (47, XXX) or polysomy X (49, XXXXY). As much as number of X chromosome is higher, as much mental retardation is more severe.

b) structural chromosomal abnormalities:

Wolf Hirschhorn syndrome (del 4p), Cri du Chat Syndrome (del5p), Pallister-Killian Syndrome (tetrasomia 12P), partial monosomic or trysomic syndromes, submicroscopical syndromes, etc.

c) syndromes characterized by microdeletions

Prader Willi syndrome (15q11-q12), Angelman syndrome (15q11-q12), Williams syndrome (7p13.3), Rubinstein-Taybi syndrome (16p13.3), DiGeorge syndrome (deletion 22q11), Miller Dieker Syndrome (de17p13.3), Smith Magenis Syndrome (del17p11.2).

Cri du Chat Syndrome
Prader Willi Syndrome

Angelman syndrome

Fragile X Syndrome (Covic et al.,2004)

It is now around 2% of patients with RM (both sexes), predominantly in males, occurs in 4.1% of severe cases of MR and 1% of cases of easy mental retardation and borderline

There are certain criteria that lead to the requirement of the test for fragile X syndrome:
1. presence of MR family history (affected male relative, female unaffected)
2. mandible and prominent ears
3. hiperlaxity of joints
4. weakness / hostile attitude
5. avoiding eye contact

Cytogenetic examination (Moescher et al., 2006)

1 from 10 patients with mental retardation have a diagnosis after this investigation. Cytogenetic tests are mandatory for all children who have delayed development even if there are no signs indicating a mental retardation.

FISH analysis of subtelomeric regions (Moescher et al., 2006)

FISH technique has led to knowledge of the etiology of nearly 7.4% of moderate and severe MR, with apparently normal karyotype and 0.5% of easy MR. Their cause is rearranging of telomers.

### Table 4

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<th>Chromosome Syndrome</th>
<th>Key Features</th>
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| 1pter deletion      | Growth retardation; mental retardation; seizures; visual problems; large anterior fontanelle; asymmetric and low-set, dysplastic ears; deep-set eyes; depressed nasal bridge; pointed chin; and fifth finger clinodactyly
| 1p36.3 deletion     | Ebstein anomaly; mental retardation
| 1qter deletion      | Microcephaly; growth and mental retardation; corpus callosum abnormalities; cardiac anomalies; hypospadias; characteristic facial features
| 22qter deletion     | Developmental delay; hypotonia; absent speech; and normal growth or somatic overgrowth |

Clinical presentation of patients affected by subtelomeric anomalies

Facial aspects and specific malformations in patients with criptic subtelomeric anomalies. (a) round face, low frontal hairline, hypertelorism and synophris; (b) epicanthal folds, upslanting palpebral fissures and low-set ears; (c-d) mild trigonocephaly (e-f) plagiocephaly, palpebral ptosis. (g-h-i) macrotia (l-m-n-o) severe hypertelorism, epicanthal folds and right external ear malformation; (p-q) flat face, low-set ears and foot malformation; (r) the coarse face.

2. Metabolic diseases  (Moescher et al., 2004; van Karnebeek et al., 2005)
Inborn errors of metabolism are a rare cause of mental retardation, about 1% (ranging from 0.2% to 8.4%), especially when there are no signs to suggest a metabolic disease.
Screening for metabolic diseases becomes important when targeted on a specific disease category.
In conclusions: the key steps in the investigation of mental retardation are:

- Family history, medical history and physical exam, regardless of the severity of MR are required.
- The plurimarformativ syndrome, mental retardation of moderate / severe undiagnosed, requires a standard cytogenetic examination.
- FISH examination is mandatory while the karyotype is apparently normal on patient with mental retardation.
- Test for fragile X syndrome is compulsory for boys and girls when they have a family history of mental retardation, diagnosis of this syndrome becomes more likely with increasing severity of MR.
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